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GUIDELINE COMMENTARY

Antiplatelet and Anticoagulant Therapy in the 2025 ACC/AHA Guideline for Acute Coronary Syndromes

Key Recommendations

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The 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes (ACS),[1] published in this issue of *JACC*, replaces the prior U.S. guidelines on the management of ST-segment and non-ST-segment elevation ACS.[2,3] The new guideline provides an excellent evidence-based framework for diagnosis and management of type I ACS (ie, in the setting of atherothrombosis). This Guideline Commentary highlights the key recommendations related to antithrombotic therapy, compares the 2025 guideline with prior American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC) recommendations, and offers reflections on recent changes and opportunities for further clarification.

With respect to antiplatelet therapy, early initiation of aspirin and an oral $P2Y_{12}$ receptor inhibitor remain Class 1 recommendations. The new guideline recommends either ticagrelor or prasugrel (Class 1, without distinction between the two) as the preferred $P2Y_{12}$ inhibitor in ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI). If these agents are contraindicated, not tolerated, unaffordable, or unavailable, clopidogrel is recommended. The initiation of oral $P2Y_{12}$ inhibitors before transfer to the catheterization laboratory is recommended if there is an expected delay of >24 hours (Class 2b). In patients undergoing percutaneous coronary intervention (PCI) who have not received a $P2Y_{12}$ inhibitor, intravenous cangrelor may be reasonable (Class 2b). The recommendations for the duration of dual antiplatelet therapy (DAPT) following ACS are more nuanced: The guideline recommends a default DAPT duration of 1 year after ACS for patients without high bleeding risk

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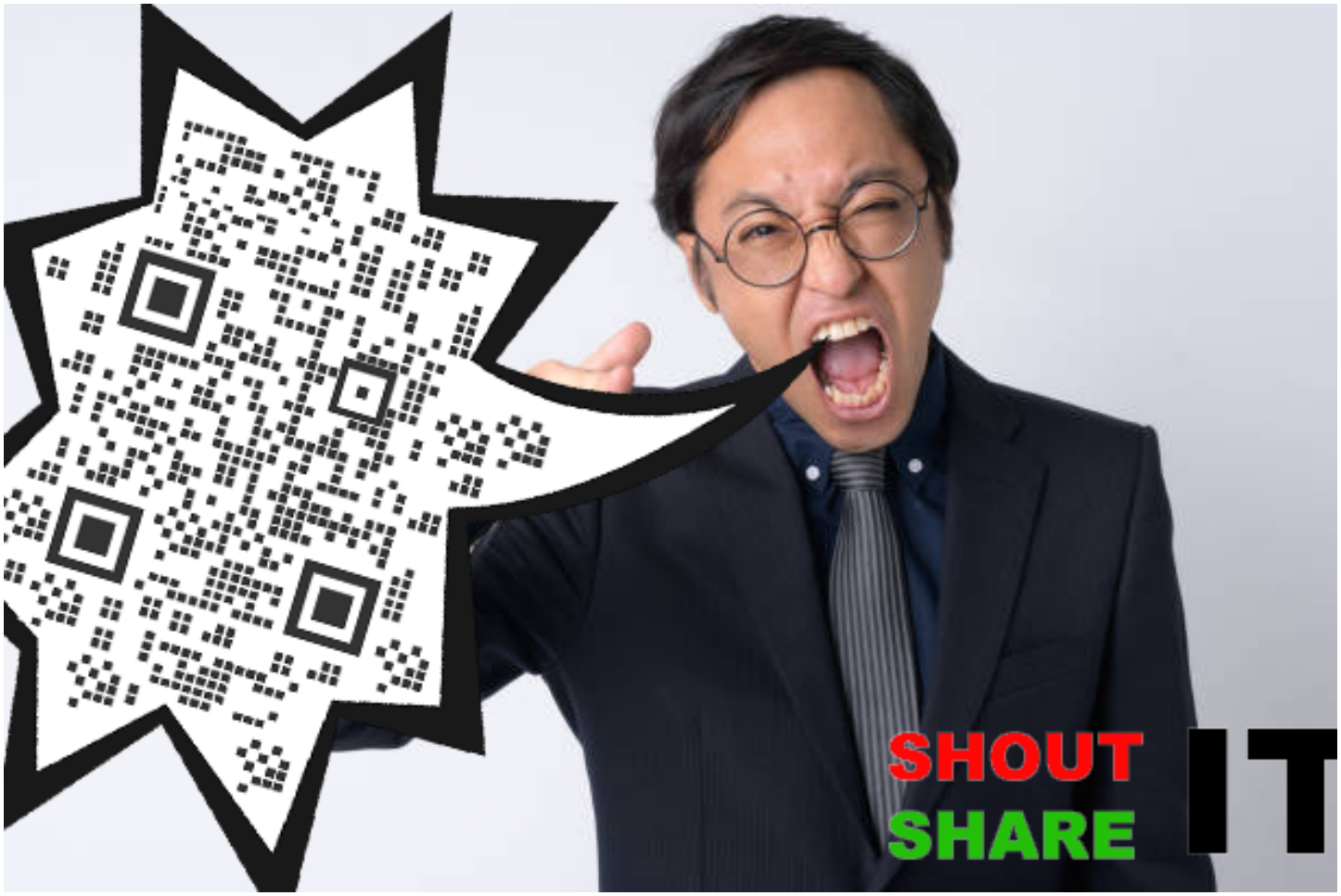
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(Class 1), but where bleeding risk is a concern, it recommends ticagrelor monotherapy 1 month after PCI (Class 1) (Figure 1A). Clopidogrel-based DAPT is recommended for patients with STEMI who receive fibrinolytic therapy. In patients with NSTEMI who undergo medical therapy alone, the guideline gives a Class 1 recommendation for aspirin and ticagrelor.

As for anticoagulation, parenteral anticoagulation in all individuals presenting with ACS is an unchanged Class 1 recommendation. For patients intended to be treated with PCI, a Class 1 recommendation is given for parenteral anticoagulation until revascularization is performed. Although the guideline provides a Class 1 recommendation for unfractionated heparin (UFH) to support PCI in STEMI, it also provides a Class 1 recommendation for bivalirudin to reduce mortality and bleeding in STEMI (compared with UFH), in which case a high-dose post-PCI bivalirudin infusion should be considered. For NSTEMI, UFH receives a Class 1 recommendation. The guideline provides a Class 2b recommendation for considering bivalirudin in non-ST-segment elevation ACS to reduce bleeding ("as an alternative," ie, compared with UFH) and recommends against fondaparinux (Class 3) in PCI because of the risk of guide catheter thrombosis.[4] In patients who require continued anticoagulation for another indication, abbreviated DAPT (for 1-4 weeks) followed by anticoagulation plus antiplatelet monotherapy (preferentially clopidogrel) received a Class 1 recommendation. This is supported by findings from 4 randomized trials of direct oral anticoagulants for AF and ACS or PCI.

Figure 1B compares the recommendations for antithrombotic therapy for patients with ACS undergoing PCI in the new 2025 guideline to those from the ESC in 2023 and the ACC/AHA 2013 STEMI and 2014 non-ST-segment elevation ACS guidelines. To facilitate the comparison, these recommendations are summarized at the presentation (before arrival to the catheterization laboratory), within the catheterization laboratory, and after PCI (including post-discharge). Some differences between the guidelines are related to evolving evidence, such as the cumulative data on the safety of shorter DAPT duration, particularly with newer stent technology and routine use of intravascular imaging that reduces the risk of stent thrombosis. Other differences are related to differences in the interpretation of the existing evidence by guideline committees, such as the preference of prasugrel over ticagrelor by the ESC based on a single large, open-label clinical trial,[5] compared with equal weighting in the 2025 ACC/AHA guideline.

The great value of the 2025 ACS guideline notwithstanding, 4 thematic issues deserve further attention. First, some recommendations may benefit from clarification to improve internal alignment. For example, the guideline includes Class 1 recommendations both for DAPT for 1 year (to reduce ischemic events) and for switching to ticagrelor monotherapy after 1 month of tolerating DAPT (to reduce bleeding). Although these recommendations likely indicate individualized decision-making, for a single patient in front of a nonexpert clinician, which of the Class 1 recommendations should be prioritized? Similarly, for anticoagulant therapy, the guideline gives a Class 1 recommendation for UFH in STEMI to reduce ischemic events, followed by another Class 1 recommendation for bivalirudin (over UFH) to reduce ischemic events and mortality. If bivalirudin is superior to UFH, why does UFH receive a Class 1 recommendation? Second, some key questions are either omitted or not discussed with details inclusive of recommendation class. For example, the 2025 guideline does not address type 2 myocardial infarction. The guideline shares an ungraded recommendation for continued chewable vs coated aspirin, although this recommendation is not supported by clinical trial evidence.[6] The guideline does not opine on whether aspirin dosing should be weight-based[7] or offer detailed recommendations on whether and when the choice of oral $P2Y_{12}$ inhibitors should be guided by genetic or functional tests.[8] As for anticoagulant therapy, emerging data question the utility of routine postprocedural anticoagulation. The guideline does not comment on this regimen,[9] including whether hospitalized patients with ACS should receive postprocedural prophylactic anticoagulation. Third, reasons behind some recommendations could be further clarified. For example, in pooled analysis of clinical trials, cangrelor reduced periprocedural ischemic events compared with clopidogrel. The 2b recommendation in the 2025 guideline is likely related to attenuated benefit compared with pre-catheterization laboratory use of clopidogrel, limited data vs prasugrel or ticagrelor, excess drug costs, and concerns for improper transition from cangrelor to an oral $P2Y_{12}$ inhibitor. Finally, the guideline does not share recommendations based on sex, race, or ethnicity, which may affect disease presentation, treatment strategies, and outcomes through biological and environmental pathways. These issues may be further clarified in future focused updates.

In conclusion, the 2025 ACC/AHA guideline for diagnosing and managing ACS provides thoughtful,

ABBREVIATIONS AND ACRONYMS

DAPT = dual antiplatelet therapy

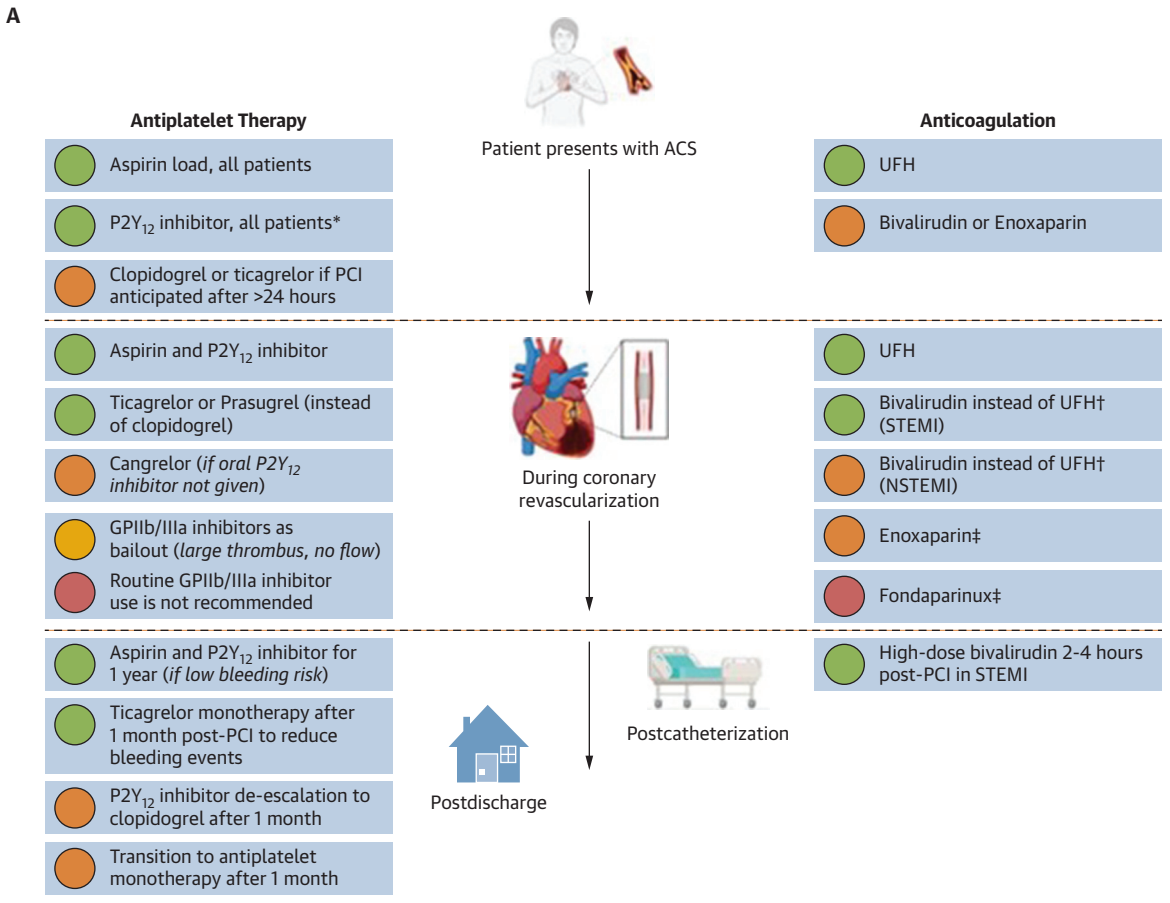
NSTEMI = non-ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

UFH = unfractionated heparin

FIGURE 1 Summary of Selected Recommendations for Antiplatelet and Anticoagulant Therapy in the 2025 ACC/AHA Guideline for ACS, and Their Comparison With Prior ACC/AHA and ESC Guidelines


A
Antiplatelet Therapy
Aspirin load, all patients
P2Y12 inhibitor, all patients*
Clopidogrel or ticagrelor if PCI anticipated after >24 hours
Aspirin and P2Y12 inhibitor
Ticagrelor or Prasugrel (instead of clopidogrel)
Cangrelor (if oral P2Y12 inhibitor not given)
GPIIb/IIIa inhibitors as bailout (large thrombus, no flow)
Routine GPIIb/IIIa inhibitor use is not recommended
Aspirin and P2Y12 inhibitor for 1 year (if low bleeding risk)
Ticagrelor monotherapy after 1 month post-PCI to reduce bleeding events
P2Y12 inhibitor de-escalation to clopidogrel after 1 month
Transition to antiplatelet monotherapy after 1 month
Patient presents with ACS
During coronary revascularization
Postcatheterization
Postdischarge
Anticoagulation
UFH
Bivalirudin or Enoxaparin
UFH
Bivalirudin instead of UFH† (STEMI)
Bivalirudin instead of UFH† (NSTEMI)
Enoxaparin‡
Fondaparinux‡
High-dose bivalirudin 2-4 hours post-PCI in STEMI

(A) Summary of selected recommendations for antiplatelet and anticoagulant therapy in the 2025 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline for Acute Coronary Syndrome (ACS), and (B) their comparison with prior ACC/AHA and European Society of Cardiology (ESC) guidelines. *If planned for percutaneous coronary intervention (PCI) within 24 hours, $P2Y_{12}$ inhibitor administration can be deferred until coronary anatomy has been defined. †No strong evidence is available in medically managed patients with ACS. ‡In patients with ACS managed with medical therapy, enoxaparin, and fondaparinux are recommended in favor of unfractionated heparin (UFH). §The ESC 2023 guideline recommended fondaparinux, not enoxaparin, in patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS) in whom early invasive angiography (<24 h) is not anticipated.[10] ¶Ticagrelor is also recommended by the ACC/AHA 2025 and ESC 2023 guidelines in patients with ACS not undergoing PCI (Class 1).[1,10] Moreover, prasugrel should not be administered in patients with a history of stroke or transient ischemic attack (Class 3).[1,10] Maintenance dose reduction for prasugrel should be considered for patients with body weight <60 kg or age ≥75 years.[1] #The 2014 ACC/AHA guideline mentioned that using ticagrelor in preference to clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy is reasonable (Class 2a).[2] ‖The ESC 2023 guideline mentioned that in patients aged 70-80 years, especially with high bleeding risk, clopidogrel as the $P2Y_{12}$ inhibitor may be considered (Class 2b).[10] **The ESC 2023 guideline mentioned that in patients with high bleeding risk, aspirin or $P2Y_{12}$ receptor inhibitor monotherapy after 1 month of dual antiplatelet therapy (DAPT) may be considered (Class 2b).[10] BARC = Bleeding Academic Research Consortium; BRIGHT-4 = Bivalirudin With Prolonged Full Dose Infusion Versus Heparin Alone During Emergency PCI; CHAMPION-PHOENIX = A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention; CLARITY-TIMI 28 = CLopiodogrel as Adjunctive ReperfusIon TherapY-Thrombolysis In Myocardial Infarction; COMMIT = Randomized, Placebo-Controlled Trial of Adding Clopidogrel to Aspirin in 46,000 Acute Myocardial Infarction Patients; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial; IPD = individual participant data; ISAR-REACT 5 = Prospective, Randomized Trial of Ticagrelor Versus Prasugrel in Patients With Acute Coronary Syndrome; MACE = major adverse cardiovascular events; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; OASIS-5 = Fifth Organization to Assess Strategies in Acute Ischemic Syndromes trial; PLATO = PLATelet inhibition and patient Outcomes; SAPT = single antiplatelet therapy; STEMI = ST-segment elevation myocardial infarction; TICO = Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome; T-PASS = Ticagrelor Monotherapy in PAtients Treated With New-generation Drug-eluting Stents for Acute Coronary Syndrome; TRITON-TIMI 38 = Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38; TWILIGH-ACS = Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention-Acute Coronary Syndromes; ULTIMATE-DAPT = One-Month Ticagrelor Monotherapy After PCI in Acute Coronary Syndromes-dual antiplatelet therapy.

Continued on the next page

FIGURE 1 Continued

B

		ACS: Antiplatelet and Anticoagulant Therapy	ACC/AHA 2025	ACC/AHA 2013-2014	ESC 2023	Evidence Summary
Before PCI	Antiplatelet	Pretreatment with $P2Y_{12}$ inhibitor in patients with NSTE-ACS planned for an invasive strategy anticipated to occur ≥24 hours after	✓	?	✓	CURE trial substudy: ↓ MACE with clopidogrel pretreatment vs placebo
		Cangrelor in $P2Y_{12}$ receptor inhibitor-naive patients undergoing PCI (especially those unable to receive oral therapy)	✓	?	✓	CHAMPION-PHOENIX/-PLATFORM/-PCI: ↓ ischemic events but ↑ minor bleeding with cangrelor vs clopidogrel or placebo
During PCI	Anticoagulant	Parenteral anticoagulation (using UFH) during primary PCI in STEMI and for other patients with ACS at the time of diagnosis	✓	✓	✓	UFH has traditionally been the preferred anticoagulant to support PCI
		Bivalirudin with high-dose post-PCI infusion as an alternative to UFH in patients with STEMI undergoing primary PCI	✓	?	✓	BRIGHT-4 trial: ↓ death or BARC types 3-5 bleeding and stent thrombosis with bivalirudin vs. heparin (similar results in a recent IPD meta-analysis of 6 trials)
		Bivalirudin as an alternative to UFH in patients with NSTE-ACS undergoing primary PCI	✓	?	?	IPD meta-analysis of 5 trials: no differences in mortality or ischemic events but ↓ serious bleeding with bivalirudin vs heparin
		Fondaparinux or enoxaparin in patients with NSTE-ACS in whom early invasive angiography (<24 hours) is not anticipated	✓	✓	✓§	OASIS-5 trial: Similar risk of ischemic events but ↓ major bleeding with fondaparinux vs enoxaparin
After PCI	Antiplatelet	DAPT with aspirin and $P2Y_{12}$ inhibitors for 12 months in patients without high bleeding risk	✓	✓	✓	Supported by the CLARITY-TIMI 28, COMMIT, and CURE trials
		Preference of ticagrelor and prasugrel over clopidogrel in patients proceeding to PCI	✓¶	?#	✓¶	TRITON-TIMI 38 & PLATO trials: ↓ MACE but ↑ major bleeding with prasugrel or ticagrelor vs clopidogrel
		Preference of prasugrel over ticagrelor in patients who proceed to PCI	?	?	✓	ISAR-REACT-5 trial: ↓ MACE without increased major bleeding with prasugrel vs ticagrelor
		Clopidogrel when prasugrel/ticagrelor are unavailable, cannot be tolerated, or are contraindicated	✓	?	✓‖	Supported by the CLARITY-TIMI 28, COMMIT, and CURE trials
		De-escalation from DAPT to SAPT with ticagrelor after 1 month in patients at high bleeding risk post PCI	✓	?	✓**	TWILIGHT-ACS, ULTIMATE-DAPT, T-PASS, TICO trials: ↓ bleeding without excess in MACE with ticagrelor alone (vs continued DAPT) after 1-3 months

✓ Recommended as Class 1 ✓ Suggested as Class 2a ✓ Considered as Class 2b Not Recommended (Class 3) ? Not Addressed

practical, and actionable recommendations for antithrombotic therapy. When paired with available resources and individual characteristics and values of patients, they can help clinical practice and medical practitioners until further data emerges.

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